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PATENT SPECIFICATION

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COMPLETE SPECIFICATION (AMENDED).

An Improved Process for the Production of Hormone Preparations.

We, "PHARMAGANS" PHARMACEUTISCHES INSTITUT, LUDWIG WILHELM GANS A.G., of Oberursel, a/Taunus, Germany, a German Company, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

It is known that desoxycholic acid has the property of forming addition compounds with certain well defined compounds, such as hydrocarbons, ketones, aldehydes, phenols.

We have now found that hormone preparations of ready resorbability, and capable of being administered through the mouth, may be produced by causing hormones or salts, or salt-like compounds, of hormones, or substances containing hormones or compounds of hormones to react with desoxycholic acid, or other bile acids, or salts or esters of the same. In carrying out this process the reaction components may be allowed to act on one another in presence of aqueous or non-aqueous solvents or mixtures of solvents, if necessary in presence of solution promoters. Suitable hormones which may be employed in the process according to the invention are, for example, adrenalin, thyroxin, insulin, and sexual hormones. Endocrine gland preparations offer an example of substances containing hormones which may be employed in the invention. Cholic acid may be given as a further example of a bile acid; it may be used as such, or in the form of an ester or salt.

In carrying out the invention the hormone, e.g. insulin, may be allowed to interact with desoxychlolic acid or cholic acid in presence of solvents, e.g. in such a way that one of the compounds is dissolved in a solvent and the other is introduced in dissolved or undissolved form. Thus, for example, by introduction of insulin in the finely divided state into an aqueous solution of desoxycholic acid the water soluble addition compound may be obtained. Instead of water the following may also be used as solvent if necessary: aqueous solutions, e.g. salt solutions, or organic solvents, such as alcohol, acetic ether, acetone, glacial acetic acid and the like, or even mixtures of various solvents, e.g. of aqueous and non-aqueous solvents. As solvents or solution promoters come into consideration amongst other things also lipoids (glycerides, phosphatides), fats, oils, fatty acids, e.g. oleic acid, stearins, or mixtures of such with one another, or mixtures of such with solvents, such as alcohol, glacial acetic acid or the like.

For example, desoxycholic acid, cholic acid or a salt of these acids, may be dissolved in a suitable solvent, e.g. glacial acetic acid, and a hormone added, e.g. adrenalin. Also, for example, a solution containing adrenalin on the one hand and a solution of, for example, cholic acid in glacial acetic acid on the other hand, may be introduced into oleic acid or ground nut oil. In this manner preparations may be obtained which are soluble in lipoids, oils fats, oleic acid, and the like, and more particularly are absorbable.

If desired the components may also be brought into interaction in more or less fine subdivision, e.g. colloidal dispersion, in a suitable aqueous or non-aqueous dispersion medium. For producing the desired degree of dispersion the known devices may be used such as, for example, colloid mills or, for example, chemical or physical precipitating processes also.

In many cases the addition compound

does not form immediately but only after a certain time which varies within certain limits according to the nature of the components and the working conditions, e.g. as regards the solvent, concentration of the solution, temperature and so forth.

Addition substances, e.g. such which are suitable for producing curative effects (e.g. lipoids or phosphatides with vitamine effects) or for raising the stability or absorbability of the preparations (e.g. benzoic acid, alcohol, chloroform) or for improving the odour or flavour (e.g. sugar, vanillin, almond oil) and the like, may be incorporated, during or after the combination of the components, with the preparations which can be produced according to the invention.

The invention enables hormone preparations to be produced which possess other, in part better, properties than those of the hormones serving as initial materials or the hormone-like or hormone-containing bodies or substances. For example, hormones which are insoluble or difficulty soluble, in water, may be converted into addition compounds which are readily soluble in water, or hormones, which are insoluble or difficultly soluble in other solvents, such as, for example, oils, may be converted into an oil-soluble form, if necessary with the coaction of so-called solution promoters.

More particularly it is also possible to convert hormones, which hitherto could be successfully employed only, for example, by injection, into preparations which can be administered internally and thereby produce characteristic effects. Thus, for example, insulin which hitherto could be employed only subcutaneously, may be administered internally in the form of addition compounds, for example, with desoxycholic acid, and in this way effects may be produced which principally differ from the effects of insulin administered subcutaneously. The addition compounds are capable of producing permanent effects, lasting, for example, for several weeks probably because they are stored up in the organism and are given up as required. Moreover in comparison to insulin administered subcutaneously they produce a raising of the tolerance with respect to carbohydrates. Further advantages are that there is no danger of over-dosing and shock effect.

EXAMPLES:

1. The quantity of insulin corresponding by weight to 10,000 units is brought into solution with, for example, 1 grm of sodium salt of desoxycholic acid which is dissolved in just so much distilled water as corresponds to the desired final concentration.

2. The quantity of insulin corresponding by weight to 10,000 units is brought into solution, for example, with 1 grm of cholic acid which is dissolved in just as much distilled water as corresponds to the desired final concentration.

3. The quantity of insulin corresponding by weight to 10,000 units is brought into solution, e.g. with 1 grm of purified bile, which is dissolved in just as much distilled water as corresponds to the desired final concentration.

4. The quantity of insulin corresponding by weight to 10,000 units is brought into solution, for example, with 6 grms of cholic acid which have been dissolved, for example, in 50 ccm of glacial acetic acid and this solution is introduced slowly and with agitation into as much oleic acid as corresponds to the desired final concentration.

5. The quantity of insulin corresponding by weight to 10,000 units is dissolved for example, in a solution of 6 grms of cholic acid in 50 ccm of glacial acetic acid. This solution is introduced slowly, and with agitation, into a quantity of ground nut oil which corresponds to the desired final concentration, and which previously has been mixed with a solution of 6.0 grms of cholic acid in 50 ccm of glacial acetic acid.

6. 0.5 grm of adrenalin are brought into solution e.g. with 1 grm of the sodium salt of desoxycholic acid which is dissolved in as much distilled water as corresponds to the desired final concentration.

7. 0.5 grm of adrenalin are brought into solution with 1 grm of cholic acid which has been dissolved, for example, in 15 ccm of glacial acetic acid, and this solution is introduced slowly and with agitation into just as much oleic acid as corresponds to the desired final concentration.

8. 0.5 grm of adrenalin are brought into solution with 1 grm of cholic acid which has been dissolved, for example, in 15 ccm of glacial acetic acid and this solution is introduced slowly and with agitation, for example, into as much ground nut oil as corresponds to the desired final concentration. Before the introduction of the adrenalin solution the ground nut oil is mixed with a solution of, for example, 6.0 grms of cholic acid in 50 ccm of glacial acetic acid.

We are aware of Specification No. 357,555, and we do not claim anything which is claimed therein.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to

be performed, we declare that what we claim is:—

1. 'A process for producing hormone preparations which are characterised by, for example, ready resorbability and capability of administeration through the mouth, consisting in this, that hormones or salts, or salt-like compounds of hormones, or substances containing hormones or compounds of hormones are caused to react with desoxycholic acid, or other bile acids, or salts or esters of the same, for example in such a way that the reaction components are allowed to act on one another in presence of aqueous or non-aqueous solvents or mixtures of solvents, if necessary in presence of solution promoters.

2. A process for the production of hormone preparations, as claimed in claim 1, characterised by the feature that insulin is converted into addition compounds by treatment with bile acids, such as desoxycholic acid, or salts or esters of bile acids.

3. The improved process for the production of hormone preparations substantially as hereinbefore described.

Dated this 20th day of March, 1930.

MARKS & CLERK.

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